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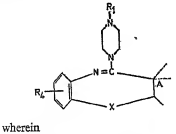
(54) PROCESS FOR THE PRODUCTION OF 6-PIPERAZINYL-MORPHANTHRIDINES AND RELATED TRICYCLICS

(71) We, WANDER LTD., of 115 Monbijoustrasse, 3001 Berne, Switzerland, a Swiss Body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to a new process for the production of compounds of formula I,



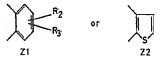
I

wherein

R_1 is hydrogen, alkoxyalkyl of 2 to 6 carbon atoms in the aggregate thereof, alkyl of 1 to 4 carbon atoms, hydroxyalkyl of 1 to 4 carbon atoms, or acyloxyalkyl of 3 to 22 carbon atoms in the aggregate thereof,

R_4 is hydrogen, alkyl, alkoxy or alkylthio, wherein the alkyl groups have 1 to 4 carbon atoms, halogen, or trifluoromethyl, and

A signifies the structure



Z1 Z2

whereby

a) when A denotes Z1, X is a $-CH_2-$, $-\overset{|}{N}-$, $-O-$, $-S-$, $-\overset{|}{N}H$ or $-\overset{|}{N}$-alkyl group wherein the alkyl group has 1 to 3 carbon atoms,

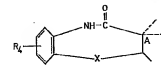
R_3 is hydrogen, alkyl, dialkylaminosulphonyl, alkylsulphonyl, wherein the alkyl groups have 1 to 4 carbon atoms, alkoxy or alkylthio of 1 to 4 carbon atoms, halogen, nitro, trifluoromethylsulphonyl, trifluoromethoxy, trifluoromethylthio, acetyl, cyano or trifluoromethyl, and

R_4 is hydrogen, halogen or alkyl of 1 to 4 carbon atoms, or

b) when A denotes Z2, X is a $-CH_2-$ or $-S-$ group.

In the substituents R_2, R_3 and R_4 halogen preferably denotes chlorine or bromine, especially chlorine. When the hydroxyalkyl group of the substituent R_1 is acylated, the acyl group preferably contains at most 18 carbon atoms, especially at most 10 carbon atoms. The acyl group is preferably aliphatic and may be saturated or unsaturated.

In accordance with the invention a compound of formula I may be obtained by a process comprising reacting a compound of formula II,



II

wherein

X, A and R_3 are as defined above, with a metal-amine complex comprising titanium, zirconium, hafnium or vanadium, and a compound of formula III,

III

wherein

R_1 is as defined above the metal-amine moiety of the complex being obtainable by reacting titanium, zirconium, hafnium or vanadium respectively in tetrahalide form with a compound of formula III. It will be appreciated that this metal amine complex can be formed in other ways.

A resulting compound of formula I wherein R_1 is acyloxyalkyl may be saponified to produce a compound of formula I wherein R_1 is hydroxyalkyl. A resulting compound of formula I wherein R_1 is hydroxyalkyl may be esterified to produce a compound of formula I wherein R_1 is acyloxyalkyl.

One preferred method of effecting the process of the invention comprises reacting a compound of formula II with a metal-amine complex in the presence of an acid-binding agent other than the compound of formula III. A tertiary amine, e.g. triethylamine, pyridine, dimethyl - aniline or an excess of a compound of formula III may be used as acid-binding agent. At least one mol, preferably, however, at least two mols of the acid-binding agent should be used, calculated on one mol of metal-amine complex.

The reaction is conveniently effected in an organic solvent, e.g. an aromatic hydrocarbon solvent such as toluene, a halogenated aromatic hydrocarbon solvent such as chlorobenzene, a halogenated aliphatic hydrocarbon solvent such as dichloroethane, or preferably an ether such as anisole. The reaction temperature is not critical within wide limits, and is conveniently from 20°C to 150°C, preferably from 50 to 120°C.

The metal-amine complex used for the reaction of the invention is preferably obtained by reaction of a halide, preferably the tetrachloride or tetrabromide of titanium, zirconium, hafnium or vanadium with a compound of formula III, before contact with a compound of formula II, conveniently at a mol ratio of 1:4 respectively. The reaction is conveniently effected in the solvent subsequently used for the reaction between a compound of formula II and the metal-amine complex. The metal halide may be used in the form of a soluble (mono- or di) etherate thereof, preferably the anisole dietherate.

It is preferred to use titanium and zirconium and especially titanium. For example titanium and zirconium in tetravalent form may be used.

After the reaction, the compound of formula I may be isolated in conventional manner. The largely insoluble metal compounds present in the reaction mixture may be conveniently removed by conversion into soluble form by the addition of an alcohol, e.g. isopropanol, and by subsequent precipitation by the addition of aqueous ammonia. The compounds of formula I, obtained in accordance with the invention, may be isolated in known manner for example by crystallization from the reaction mixture from which metal compounds have been removed, after concentrating the reaction mixture, and may be subsequently purified in known manner, e.g. by re-crystallization from isopropanol.

When a compound of formula I wherein R_1 is hydroxyalkyl is produced, the reaction product may be obtained in colloidal form, since the hydroxyalkyl group can also react with the metal halide with ester formation. In order to avoid the appearance of too much gelatinous material, which could disturb the course of the reaction, it is convenient to effect the reaction in the presence of a large amount of solvent, e.g. chlorobenzene or anisole, preferably in the presence of an excess (10- to 20-fold molar excess) of a tert.amine, e.g. triethylamine.

A compound of formula I wherein R_1 is hydroxyalkyl may alternatively be obtained by alkaline saponification of a compound of formula I wherein R_1 is an acylated hydroxyalkyl group, e.g. with a dilute sodium hydroxide solution.

The esterification of a compound of formula I wherein R_1 is hydroxyalkyl may be effected in known manner, e.g. with a reactive acid derivative, e.g. a halide of a corresponding acid, in a solvent such as chloroform, conveniently in the presence of an acid-binding agent such as triethylamine, at room temperature.

Free base forms of the compounds of formula I produced in accordance with the invention may be converted into their acid addition salt forms in conventional manner and *vice versa*. Examples of suitable salts are the hydrochlorides, hydrobromides, sulphates, fumarates, maleates and *p* - toluenesulphonates.

The compounds of formula II, used as starting materials in the process according to

the invention, are known or may be produced according to known methods or according to methods described in the Examples hereafter for the production of 10H - thieno[3,2 - c][1]benzazepines, or according to methods analogous to any of these methods.

The compounds of formula III, used as starting materials in the process according to the invention are known or may be prepared according to known methods or according to methods described in the Examples hereafter for the production of 1 - *tert* - butylpiperazine, or according to methods analogous to any of these methods.

For example a compound of formula III wherein R_1 is acyloxyalkyl may be obtained by reacting N - benzylpiperazine with a halo-alcohol, esterifying the hydroxy group of the N - benzyl - N′ - hydroxy - piperazine with a reactive acid derivative, e.g. a halide, especially the chloride of a corresponding acid, and subsequently removing the benzyl group from the resulting compound hydrogenolytically.

Compounds of formula I produced in accordance with the present invention are in general known.

Such compounds are said to exhibit pharmacological properties, e.g. central nervous system activity, some compounds, e.g. 2 - chloro - 11 - (4 - methyl - 1 - piperazinyl)-dibenzo[b,f] [1,4]thiazepine, being indicated for use as antipsychotic agents. Alternatively such compounds may be used as intermediates to produce further, e.g. heterotricyclic, compounds.

Compounds of formula I not specifically described in the literature are therefore indicated for use in a manner similar to known compounds of formula I.

In the general formula I, when A denotes Z1, the substituent R_2 is preferably in the 2 or 3 position, the substituent R_2 is preferably in the 4 position, and, when A denotes Z1 or Z2, the substituent R_4 is preferably in the position 7 or 8, i.e. meta or para to the group or atom X.

In the following non-limitative Examples all temperatures are indicated in degrees Centigrade, room temperature is a temperature between 20 and 30°C, unless otherwise indicated.

EXAMPLE 1

8 - chloro - 11 - (4 - methyl - 1 - piperazinyl) - 5H - dibenzo[b,e] [1,4]diazepine

840 cc of toluene, 90 cc of anisole and 79.2 g of titanium tetrachloride are introduced, at room temperature, in a 2.5 litre sulphonating flask provided with a dropping funnel, reflux condenser and thermometer, whereby a dark brown, clear solution is formed. A mixture of 167 g of N - methyl piperazine and 100 cc of toluene is added thereto while cooling externally with water, whereby the temperature rises to 50—55° and the amine complex, in finely divided form, forms a beige to dark brown coloured suspension. 102 g of 8 - chloro - 10,11 - dihydro - 11 - oxo - 5H - dibenzo[b,e] [1,4]-diazepine and 83 g of N - methyl piperazine are subsequently added, and the reaction mixture is heated to the boil (110—112°) for 3 hours while stirring. Cooling is then effected to 60—70°, 125 cc of isopropanol are added, whereby the insoluble titanium compounds formed during the reaction again dissolve. After the addition of 8 g of diatomaceous earth and subsequently 115 cc of concentrated ammonia (about 27%), cooling is effected to about 30° while stirring and the resulting precipitate is filtered off. The filter residue is washed with 2—3 330 cc portions of toluene. The filtrate is subsequently mixed with water, and the organic phase is extracted with dilute, approx. 10% hydrochloric acid. The base is precipitated by the dropwise addition of the hydrochloric acid extract to an excess of dilute ammonia. The precipitate is taken up in ether, the ether solution is washed with water and dried over sodium sulphate. After removal of the ether by evaporation and recrystallization from isopropanol, 8 - chloro - 11 - (4 - methyl - 1 - piperazinyl) - 5H - dibenzo[b,e] [1,4]diazepine, having a M.P. of 184—185°, is obtained.

EXAMPLE 2

6 - (4 - *tert* - butyl - 1 - piperazinyl) - morphanthridine

840 cc of toluene, 90 cc of anisole and 93.5 g of zirconium tetrachloride are introduced at room temperature into a 2.5 litre sulphonating flask provided with a dropping funnel, reflux condenser and thermometer, whereby a dark brown, clear solution is formed. A mixture of 248 g of N - *tert* - butyl piperazine and 100 cc of toluene is added thereto while cooling externally with water, whereby the temperature rises to 50—55° and the amine complex, in finely divided form, forms a dark brown coloured suspension. 87 g of morphanthridin - 6 - one and 123.5 g of N - *tert* - butyl piperazine are subsequently added and the reaction mixture is heated to the boil (110—112°) for 3 hours while stirring. Cooling is then effected to 60—70°, 125 cc of isopropanol are added, whereby the insoluble zirconium compounds formed during the reaction again dissolve. After the addition of 8 g of diatomaceous earth and subsequently 115 cc of concentrated ammonia (approx. 27%) cooling is effected to about 30° while stirring and the resulting precipitate is filtered off. The filter residue is washed with 2—3 330 cc portions of toluene. The filtrate is subsequently mixed with water and the organic phase is extracted with dilute, approx. 10%, hydrochloric acid. The base is precipitated by the dropwise addition of the

hydrochloric acid extract to an excess of dilute ammonia. The precipitate is subsequently taken up in ether, the ether solution is washed with water and dried over sodium sulphate. After removing the ether by evaporation, the residue is dissolved in acetone and 38 g of maleic acid are added to the solution. The solution is subsequently concentrated, ethyl acetate and some ether are added and the resulting precipitate is filtered off. After recrystallization from acetone/ethyl acetate/ether, the resulting 6 - (4 - *tert* - butyl - 1 - piperazinyl) - morphanthridine maleate has a M.P. of 138—141°.

The 1 - *tert* - butyl piperazine, used as starting material in the above process, may be produced as follows:

1) 1 - benzyl - 4 - *tert* - butyl piperazine

A solution of 2000 g of bis - (2 - chloroethyl) *tert* - butylamine in 500 cc of ethanol and a solution of 1095 g of benzylamine in 750 cc of ethanol are simultaneously added dropwise to 1000 cc of boiling ethanol. After the addition is complete, the reaction mixture is heated to the boil for one hour. The mixture is subsequently concentrated in a vacuum and the residue is dissolved in dilute hydrochloric acid. The acid solution is washed with ether and is subsequently rendered alkaline with a concentrated, aqueous sodium hydroxide solution. The liberated base is extracted with ether and the ether residue is distilled. 1 - benzyl - 4 - *tert* - butyl piperazine has a B.P. of 160—162° at 12 mm of Hg.

2) 1 - *tert* - butyl piperazine

348.5 g of 1 - benzyl - 4 - *tert* - butyl piperazine are dissolved in 1200 cc of 99% ethanol and 10 g of a 5% palladium/charcoal catalyst are added to the resulting solution. The solution is subsequently shaken in a hydrogenation apparatus, in a hydrogen atmosphere (1 atmosphere) and at room temperature, until the take up of hydrogen is complete. Filtration is subsequently effected, the filtrate is concentrated by evaporation in a vacuum and the residue is distilled in a vacuum. 1 - *tert* - butyl piperazine is obtained in the form of a colourless oil, having a B.P. of 66—70° at 12 mm of Hg, which crystallizes upon standing. The crystals have a M.P. of 35—40°.

By using the processes described in the above Examples 1 and 2 and the corresponding starting materials, the following compounds may be obtained in analogous manner:

5 - methyl - 11 - (4 - methyl - 1 - piperazinyl) - dibenzo[b,e] [1,4]diazepine, having a M.P. of 122—124° (from ether/petroleum ether),

2 - chloro - 11 - (4 - methyl - 1 - piperazinyl) - dibenzo[b,f] [1,4]thiazepine, having a M.P. of 116—120° (from ether/petroleum ether),

6 - (4 - methyl - 1 - piperazinyl) - morphanthridine, having a M.P. of 138—139° (from acetone/petroleum ether),

2 - methyl - 11 - (4 - methyl - 1 - piperazinyl) - dibenzo[b,f] [1,4]thiazepine, having a M.P. of 99—107° (from petroleum ether),

2 - chloro - 11 - (4 - methyl - 1 - piperazinyl) - dibenz[b,f] [1,4]oxazepine, having a M.P. of 104—110° (from petroleum ether),

2 - bromo - 11 - (4 - methyl - 1 - piperazinyl) - dibenzo[b,f] [1,4]thiazepine, having a M.P. of 138—139° (from acetone/petroleum ether),

2 - nitro - 11 - (4 - methyl - 1 - piperazinyl) - dibenz[b,f] [1,4]oxazepine, having a M.P. of 192—193° (from chloroform/acetone/petroleum ether),

2 - dimethylaminosulphonyl - 11 - (4 - methyl - 1 - piperazinyl) - dibenzo[b,f] [1,4]-thiazepine, having a M.P. of 192—193° (from acetone/petroleum ether),

2 - dimethylaminosulphonyl - 11 - (4 - methyl - 1 - piperazinyl) - dibenz[b,f] [1,4]-oxazepine, having a M.P. of 149—150° (from ether/petroleum ether),

2 - methylsulphonyl - 11 - (4 - methyl - 1 - piperazinyl) - dibenz[b,f] [1,4]oxazepine, having a M.P. of 178—179° (from acetone/ethyl/petroleum ether),

2 - trifluoromethoxy - 11 - (4 - methyl - 1 - piperazinyl) - dibenz[b,f] [1,4]oxazepine dihydrochloride monohydrate, having a M.P. of 200—210° (from alcohol/ether),

7 - chloro - 4 - (4 - methyl - 1 - piperazinyl) - thieno[2,3 - b] [1,5]benzothiazepine, having a M.P. of 162—164° (from ethyl acetate),

2 - trifluoromethylsulphonyl - 11 - (4 - methyl - 1 - piperazinyl) - dibenzo[b,f] [1,4]-thiazepine, having a M.P. of 168—170° (from ether/petroleum ether),

2 - acetyl - 11 - (4 - methyl - 1 - piperazinyl) - dibenz[b,f] [1,4]oxazepine, having a M.P. of 116—118° (from acetone/petroleum ether),

2 - trifluoromethyl - 11 - (4 - methyl - 1 - piperazinyl) - dibenz[b,f] [1,4]oxazepine, the fumarate thereof having a M.P. of 214—216° (from acetone/petroleum ether),

2 - trifluoromethylsulphonyl - 11 - (4 - methyl - 1 - piperazinyl) - dibenz[b,f] [1,4]-oxazepine, having a M.P. of 120—122° (from ether/petroleum ether),

2 - methylsulphonyl - 11 - (4 - ethyl - 1 - piperazinyl) - dibenz[b,f] [1,4]oxazepine, having a M.P. of 190—191° (from acetone/petroleum ether),

4 - (4 - methyl - 1 - piperazinyl) - thieno-[2,3 - b] [1,5]benzothiazepine, having a M.P. of 112—114° (from absolute ethanol),

4 - (4 - methyl - 1 - piperazinyl) - 10H - thieno[3,2 - c] [1]benzazepine, having a M.P. of 145—147° (from ether/petroleum ether),

8 - chloro - 4 - (1 - piperazinyl) - 10H - thieno[3,2 - c] [1]benzazepine, having a M.P. of 80—100° (from acetone/water in the presence of charcoal),

8 - chloro - 4 - [4 - (2 - acetoxyethyl) - 1 - piperazinyl] - 10H - thieno[3,2 - c] [1]-benzazepine, having a M.P. of 185—189° (from ether/petroleum ether),

8 - chloro - 4 - (4 - methyl - 1 - piperazinyl) - 10H - thieno[3,2 - c] [1]-benzazepine, having a M.P. of 193—195° (from acetone/petroleum ether),

2 - methylthio - 11 - (4 - methyl - 1 - piperazinyl) - dibenz[b,f] [1,4]oxazepine, having a M.P. of 198—201° (maleate),

4 - (4 - *tert* - butyl - 1 - piperazinyl) - 10H - thien[3,2 - c] [1]benzazepine, having a M.P. of 147—176° (maleate),

7 - methyl - 4 - (4 - methyl - 1 - piperazinyl) - 10H - thieno[3,2 - c] [1]-benzazepine, having a M.P. of 180—181° (from acetone/petroleum ether),

7 - chloro - 4 - (4 - methyl - 1 - piperazinyl) - 10H - thieno[3,2 - c] [1]-benzazepine, having a M.P. of 184—185° (from acetone),

7 - chloro - 4 - (4 - β - hydroxyethyl - 1 - piperazinyl) - 10H - thieno[3,2 - c] [1]-benzazepine, having a M.P. of 192—194° (from ethyl acetate),

8 - chloro - 4 - (4 - β - hydroxyethyl - 1 - piperazinyl) - 10H - thieno[3,2 - c] [1]-benzazepine, having a M.P. of 202—203° (from ethyl acetate),

2 - trifluoromethylsulphonyl - 11 - [4 - (β - benzamoyloxyethyl) - 1 - piperazinyl] - dibenz[b,f] [1,4]oxazepine, the oxalate thereof having a M.P. of 213—216°,

2 - trifluoromethylsulphonyl - 11 - (4 - β - hydroxyethyl - 1 - piperazinyl) - dibenz-[b,f] [1,4]oxazepine, having a M.P. of 121—123° (from ether/petroleum ether),

2 - trifluoromethylsulphonyl - 11 - (1 - piperazinyl) - dibenz[b,f] [1,4]oxazepine, having a M.P. of 183—186° (from ether),

2 - trifluoromethylsulphonyl - 11 - (4 - β - hydroxypropyl - 1 - piperazinyl) - dibenz-[b,f] [1,4]oxazepine, having a M.P. of 132—134° (from ether/petroleum ether),

2 - trifluoromethylthio - 11 - (4 - β - hydroxyethyl - 1 - piperazinyl) - dibenz-[b,f] [1,4]oxazepine, having a M.P. of 121—123° (from petroleum ether),

2 - trifluoromethylsulphonyl - 11 - (4 - β - oleyloxyethyl - 1 - piperazinyl)dibenz-β - oleyloxyethyl - 1 - piperazinyl) - dibenz-[b,f] [1,4]oxazepine,

1,4 - dimethyl - 11 - (4 - methyl - 1 - piperazinyl) - dibenz[b,f] [1,4]oxazepine, having a M.P. of 143—144° (from ether/petroleum ether),

3,4 - dimethyl - 11 - (4 - methyl - 1 - piperazinyl) - dibenz[b,f] [1,4]oxazepine, having a M.P. of 167—169° (from acetone/petroleum ether),

2,8 - dichloro - 11 - (4 - methyl - 1 - piperazinyl) - dibenz[b,f] [1,4]oxazepine, having a M.P. of 130—131° (from acetone/petroleum ether),

4,8 - dichloro - 11 - (4 - methyl - 1 - piperazinyl) - dibenz[b,f] [1,4]oxazepine, having a M.P. of 134—135° (from acetone/petroleum ether),

4 - methyl - 8 - chloro - 11 - (4 - methyl - 1 - piperazinyl) - dibenz[b,f] [1,4]oxazepine, having a M.P. of 150—151° (from ether/petroleum ether),

4 - methyl - 7 - chloro - 11 - (4 - methyl - 1 - piperazinyl) - dibenz[b,f] [1,4]oxazepine, having a M.P. of 167—168° (from acetone/petroleum ether),

2,4 - dichloro - 11 - (4 - methyl - 1 - piperazinyl) - dibenz[b,f] [1,4]oxazepine, having a M.P. of 135—138° (from acetone/petroleum ether),

2 - chloro - 11 - (1 - piperazinyl) - dibenz-[b,f] [1,4]oxazepine, having a M.P. of 178—180° (from acetone/petroleum ether).

The starting materials for the production of 10H - thieno[3,2 - c] [1]benzazepines may be obtained as follows:

4,5 - dihydro - 10H - thieno[3,2 - c] [1]-benzazepin - 4 - one

14.8 g of 2 - (2 - amino - phenyl) - thienone, 23.8 g of solid potassium hydroxide and 19.6 g of hydrazine hydrate are heated at reflux in 180 cc of diethylene glycol for 3 hours. After diluting the reaction mixture with ice water, extraction is effected with ether. The ether phase is washed thrice with water, dried over sodium sulphate and concentrated. 2 - (2 - aminobenzyl) - thiophene is obtained in the form of a light yellow oil having a B.P. of 128—130° at 0.1 mm of Hg.

46 cc of a 20% solution of phosgene in toluene are added dropwise at −3°, with stirring, to a solution of 9.8 g of the product obtained above in 60 cc of toluene. The reaction mixture is subsequently allowed to warm to room temperature while passing through a stream of phosgene, and is then heated at reflux for half an hour. After driving out the excess phosgene with a stream of nitrogen, the reaction mixture is concentrated in a vacuum and the residue is distilled. 10.8 g of 2 - (2 - isocyanato - benzyl) - thiophene, having a B.P. of 108° at 0.05 mm of Hg, are obtained.

10.5 g of 2 - (2 - isocyanato - benzyl) - thiophene (B.P. 108°/0.05 mm of Hg) are heated to 110° with 105 g of polyphosphoric acid for one hour while stirring. The reaction mixture is subsequently rendered alkaline with a concentrated ammonia solution while cool-

ing internally and externally with ice and the resulting precipitate is filtered off. This is washed with water, dried and crystallized from acetone while treating with charcoal. 4,5 - dihydro - 10H - thieno[3,2 - c] [1]-benzazepin - 4 - one is obtained in the form of grains having a M.P. of 225—236° (between 150 and 200° conversion into bright needles).

8 - chloro- or 7 - chloro - 4,5 - dihydro - 10H - thieno[3,2 - c] [1]benzazepin - 4 - one

6 g of N - *p* - toluenesulphonyl - 5 - chloro (or 4 - chloro) - anthranilic acid are heated at reflux with 10 cc of thionyl chloride for 1½ hours. After evaporating to dryness in a vacuum, the residue is recrystallized from methylene chloride/petroleum ether. The resulting N - *p* - toluenesulphonyl - 5 - chloro - anthranilic acid chloride has a M.P. of 134—136°, N - *p* - toluenesulphonyl - 4 - chloro - anthranilic acid chloride has a M.P. of 135—140°.

A solution of 6 g of stannic chloride in 10 cc of carbon disulphide is slowly added dropwise to a refluxing mixture of 7 g of finely pulverized N - *p* - toluenesulphonyl - 5 - chloro (or 4 - chloro) - anthranilic acid chloride and 3.4 g of thiophene in 25 cc of carbon disulphide. After the addition is complete, stirring is effected at room temperature for 2 hours. The solvent is subsequently evaporated in a vacuum, the residue is treated with ice water and hydrochloric acid and extracted with ethyl acetate. The ethyl acetate extract is washed with 2N hydrochloric acid, water and a saturated aqueous potassium bicarbonate solution, is dried with sodium sulphate and concentrated. The evaporation residue is treated with ether and a 1 normal aqueous sodium hydroxide solution. The aqueous alkaline solution after separation from the ether is acidified with concentrated hydrochloric acid and the resulting precipitate is drawn off by suction. The suction filter residue is washed with water and recrystallized from ethyl acetate/petroleum ether. 2 - (2 - *p* - toluenesulphonamido - 5 - chloro - phenyl) - thienone has a M.P. of 164—167°, 2 - (2 - *p* - toluenesulphonamido - 4 - chloro - phenyl) - thienone has a M.P. of 140—141°.

8.4 g of 2 - (2 - *p* - toluenesulphonamido - 5 - chloro (or 4 - chloro) - phenyl) - thienone are stirred at room temperature with 100 cc of concentrated sulphuric acid for 4 hours. The reaction product is subsequently poured on ice and the resulting mixture is rendered alkaline with a concentrated aqueous sodium hydroxide solution while cooling. A precipitate is obtained, which is taken up in ether. The ether solution is washed with water, dried with sodium sulphate and concentrated, whereby a residue is obtained. After recrystallization from ether/petroleum ether in the presence of charcoal and aluminium oxide, 2 - (2 - amino - 5 - chloro - phenyl) - thienone has a M.P. of 97—98° and 2 - (2 - amino - 4 - chloro - phenyl) - thienone has a M.P. of 66—72°.

15.5 g of 2 - (2 - amino - 5 - chloro (or 4 - chloro) - phenyl - thienone, 23.8 g of solid potassium hydroxide and 19.6 g of hydrazine hydrate are heated at reflux in 180 cc of diethylene glycol for 2 hours. After diluting the reaction mixture with ice water, extraction is effected with ether. The ether phase is washed thrice with water, dried with sodium sulphate and concentrated. 2 - (2 - amino - 5 - chloro - benzyl) - thiophene, having a B.P. of 150—157° at 0.1 mm of Hg, and 2 - (2 - amino - 4 - chloro - benzyl) - thiophene, having a B.P. of 137—140° at 0.05 mm of Hg, are obtained in the form of an oil.

46 cc of a 20% solution of phosgene in toluene are added dropwise at −3°, while stirring, to a solution of 11 g of 2 - (2 - amino - 5 - chloro (or 4 - chloro) - benzyl) - thiophene in 60 cc of toluene. The reaction mixture is subsequently allowed to warm to room temperature while introducing a stream of phosgene and is subsequently heated at reflux for half an hour. After driving off the excess phosgene with a nitrogen stream, the reaction mixture is concentrated in a vacuum and the residue is distilled. 2 - (2 - isocyanato - 5 - chloro - benzyl) - thiophene, having a B.P. of 137—139° at 0.1 mm of Hg, and 2 - (2 - isocyanato - 4 - chloro - benzyl - thiophene, having a B.P. of 124—125° at 0.05 mm of Hg, are obtained.

Ring closure of 2 - (2 - isocyanato - 5 - chloro (or 4 - chloro) - benzyl) - thiophene, using the process described above with respect to 2 - (2 - isocyanato - benzyl) - thiophene, yields 8 - chloro - 4,5 - dihydro - 10H - thieno[3,2 - c] [1]benzazepin - 4 - one, having a M.P. of 280—281° (after recrystallization from dioxane/acetone), and 7 - chloro - 4,5 - dihydro - 10H - thieno[3,2 - c] [1]benzazepin - 4 - one, having a M.P. of 264—266° (after recrystallization from acetone).

Following the procedure described in Example 1 or 2 but replacing the starting materials with appropriate compounds in equivalent amounts, the following compounds are prepared:—

2 - methoxy - 11 - (4 - methyl - 1 - piperazinyl)dibenz[b,f] [1,4]oxazepine;

2 - fluoro - 11 - (4 - methyl - 1 - piperazinyl)dibenz[b,f] [1,4]oxazepine;

2 - cyano - 11 - (4 - methyl - 1 - piperazinyl)dibenz[b,f] [1,4]oxazepine;

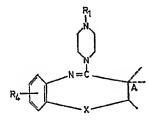
2,4 - difluoro - 11 - (4 - methyl - 1 - piperazinyl)dibenz[b,f] [1,4]oxazepine;

2,4 - dibromo - 11 - (4 - methyl - 1 - piperazinyl)dibenz[b,f] [1,4]oxazepine;

8 - methoxy - 11 - (4 - methyl - 1 - piperazinyl)dibenzo[b,f] [1,4]thiazepine;
7 - methylthio - 11 - (4 - methyl - 1 - piperazinyldibenzo[b,f] [1,4]thiazepine;
8 - fluoro - 11 - (4 - methyl - 1 - piperazinyl)dibenz[b,f] [1,4]oxazepine;
8 - bromo - 11 - (4 - methyl - 1 - piperazinyl)dibenz[b,f] [1,4]oxazepine;
8 - trifluoromethyl - 11 - (4 - methyl - 1 - piperazinyl) - 5H - dibenzo[b,e] [1,4]diazepine; and
2 - nitro - 11 - (4β - methoxyethyl - 1 - piperazinyl)dibenz[b,f] [1,4]oxazepine.

WHAT WE CLAIM IS:—

1. A process for the production of a compound of formula I,



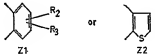
I

wherein

R_1 is hydrogen, alkoxyalkyl of 2 to 6 carbon atoms in the aggregate thereof, alkyl of 1 to 4 carbon atoms, hydroxyalkyl of 1 to 4 carbon atoms, or acyloxyalkyl of 3 to 22 carbon atoms in the aggregate thereof,

R_4 is hydrogen, alkyl, alkoxy or alkylthio, wherein the alkyl groups have 1 to 4 carbon atoms, halogen, or trifluoromethyl, and

A signifies the structure



Z1 Z2

whereby

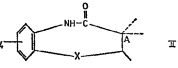
a) when A denotes Z1, X is a —CH_2—, —O—, —S—, —NH or —N-alkyl group wherein the alkyl group has 1 to 3 carbon atoms,

R_2 is hydrogen, alkyl, dialkylaminosulphonyl, alkylsulphonyl, wherein the alkyl groups have 1 to 4 carbon atoms, alkoxy or alkylthio of 1 to 4 carbon atoms, halogen, nitro, trifluoromethylsulphonyl, trifluoromethoxy, trifluoromethylthio, acetyl, cyano or trifluoromethyl, and

R_3 is hydrogen, halogen or alkyl of 1 to 4 carbon atoms, or

b) when A denotes Z2, X is a —CH_2— or —S-group,

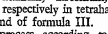
which comprises reacting a compound of formula II,



II

wherein

X, A and R_4 are as defined above, with a metal-amine complex comprising titanium, zirconium, hafnium or vanadium, and a compound of formula III,



III

wherein

R_1 is as defined above, the metal-amine moiety of the complex being obtainable by reacting titanium, zirconium, hafnium or vanadium respectively in tetrahalide form with a compound of formula III.

2. A process according to claim 1, in which the metal is titanium or zirconium in tetravalent form.

3. A process according to claim 1 or 2, in which the metal-amine complex is formed by reacting a tetrachloride or tetrabromide of the metal with a compound of formula III, before contact with the compound of formula II as defined in claim 1.

4. A process according to claim 3, in which the mol ratio of metal tetrachloride or tetrabromide to compound of formula III is substantially 1:4.

5. A process according to claim 3 or 4, wherein the metal tetrachloride or tetrabromide is in the form of a soluble etherate.

6. A process according to claim 5, wherein the etherate is that formed from anisole.

7. A process according to any preceding claim, carried out in the presence of an acid-binding agent, other than the compound of formula III as defined in claim 1.

8. A process according to claim 7, carried in which the mol ratio of acid-binding agent to metal-amine complex is at least 2:1.

9. A process according to claim 7 or 8 wherein the acid-binding agent is a tertiary amine.

10. A process according to any preceding claim, carried out in the presence of as solvent an aromatic hydrocarbon, a halogenated aromatic hydrocarbon or an ether.

11. A process according to claim 10, in which the solvent is chlorobenzene, toluene or anisole.

12. A process according to claim 10 wherein the preparation of the metal-amine complex and the reaction thereof with the compound of formula II is effected in the presence of toluene and anisole.

13. A process according to any preceding claim, carried out at a temperature from 20 to 150°C.

14. A process according to any one of the preceding claims, wherein R_8 is hydrogen.

15. A process according to any one of the preceding claims, wherein R_8 or R_4 is para to the group or atom X.

16. A process according to any one preceding claim, wherein R_1 is alkyl of 1 to 4 carbon atoms.

17. A process according to any one preceding claim, wherein R_1 is alkoxyalkyl of 2 to 6 carbon atoms in the aggregate thereof or acyloxyalkyl of 3 to 22 carbon atoms in the aggregate thereof or hydrogen.

18. A process according to any one preceding claim, wherein appropriate starting materials are used to produce 8 - chloro - 11 - (4 - methyl - 1 - piperazinyl) - 5H - dibenzo[b,e] [1,4]diazepine.

19. A process according to any one preceding claim, wherein appropriate starting materials are used to produce 2 - chloro - 11 - (4 - methyl - 1 - piperazinyl) - dibenzo-[b,f] [1,4]thiazepine.

20. A process according to any one preceding claim, wherein appropriate starting materials are used to produce 6 - (4 - methyl - 1 - piperazinyl) - morphanthridine.

21. A process according to any one preceding claim, wherein appropriate starting materials are used to produce 2 - chloro - 11 - (4 - methyl - 1 - piperazinyl) - dibenz-[b,f] [1,4]oxazepine.

22. A process according to any one preceding claim, wherein appropriate starting materials are used to produce 2 - chloro - 11 - (1 - piperazinyl) - dibenz[b,f] [1,4]-oxazepine.

23. A process according to any one preceding claim, wherein appropriate starting materials are used to produce 2 - trifluoromethylsulphonyl - 11 - (4 - β - hydroxyethyl - 1 - piperazinyl) - dibenz[b,f] [1,4]-oxazepine.

24. A process according to any one preceding claim, wherein appropriate starting materials are used to produce 6 - (4 - *tert* - butyl - 1 - piperazinyl) - morphanthridine.

25. A process according to any one preceding claim, wherein appropriate starting materials are used to produce 2,4 - difluoro - 11 - (4 - methyl - 1 - piperazinyl) - dibenz-[b,f] [1,4]oxazepine.

26. A process according to any one preceding claim, wherein appropriate starting materials are used to produce 2,4 - dibromo - 11 - (4 - methyl - 1 - piperazinyl) - dibenz-[b,f] [1,4]oxazepine.

27. A process according to any one preceding claim, wherein appropriate starting materials are used to produce 8 - fluoro - 11 - (4 - methyl - 1 - piperazinyl) - dibenz-[b,f] [1,4]oxazepine.

28. A process according to any one preceding claim, wherein appropriate starting materials are used to produce 8 - bromo - 11 - (4 - methyl - 1 - piperazinyl) - dibenz-[b,f] [1,4]oxazepine.

29. A process for the production of a compound of formula I, stated in claim 1, substantially as hereinbefore described with reference to Example 1.

30. A process for the production of a compound of formula I, stated in claim 1, substantially as hereinbefore described with reference to Example 2.

31. Compounds of formula I, whenever produced by a process according to any preceding claim.

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